IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of: Metin COLPAN
Serial No.: 08/244,530 Group Art Unit: 1803
Filed: August 2, 1994 Examiner: L. Crane
For: DEVICE AND A PROCESS FOR THE ISOLATION OF NUCLEIC ACIDS

TRANSMITTAL

Assistant Commissioner of Patents
Washington, D.C. 20231

Sir:

Transmitted herewith is a RESPONSE in the above captioned application.

___Small Entity status of this application under 37 C.F.R. 1.9 and 1.27 has been established by a verified statement previously submitted.

___A verified Statement to establish small entity status under 37 C.F.R. 1.9 and 1.27 is enclosed.

XXX No additional fee is required.

The fee has been calculated as shown below:

Claims Remaining After Amendment	Highest Number Previously Paid For	Present Extra Fee	Small Entity Rate Addit. (or) Fee	Other Than A Small Entity Rate Addit.
Total - 20 = 0		x11 = $	x 22 = $	
Indep. - 3 = 0		x39 = $	x 78 = $	
First Presentation of Multiple Dependent Claim		x125= $	x250 = $	
Total Additional Fee		$	$	

__ A check in the amount of $ is attached for:

XX If a Petition for Extension of Time is necessary and the Petition and/or the check is not enclosed, this will act as the Petition and applicant herewith petitions the Commissioner to extend the time for response and charge any fees necessary under 37 CFR 1.17 (a)-(d) to Deposit Account No. 06-1358. The Commissioner is also authorized to charge payment of any other additional fees associated with this communication or credit any overpayment to Deposit Account No. 06-1358. A duplicate copy of this sheet is attached.

Atty. Dkt. No.: 10496/P58126NA
Dated: June 5, 1996
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#14

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of:

Metin COLPAN

Serial No.: 08/244,530 Group Art Unit: 1803

Filed: August 2, 1994 Examiner: L. Crane

For: DEVICE AND A PROCESS FOR THE ISOLATION OF NUCLEIC ACIDS

RESPONSE

Assistant Commissioner of Patents
Washington, D.C. 20231

Sir:

Applicant submits the present response to the Office Action dated March 5, 1996.

Claims 40-61 are presently active.

The claims stand rejected as allegedly unpatentable under 35 U.S.C. 103 based on the teachings of Henco combined with Little, Hagen combined with Sternberg and Henco, and Sternberg combined with Henco and Little. Reconsideration is respectfully requested.

The process according to claims 40 to 59 saliently differs from Henco in that steps c) and d) of claim 40 are neither taught nor suggested. Henco contains no motivation to modify the process disclosed in therein by the steps c) and d) of present claim 40. No hint is given in Henco that (i) an increase in salt concentration should be effected in the sample fraction, nor is there any hint that (ii) such a fraction should be subsequently treated by application to a mineral support material in order to bind thereto the nucleic acid contained in the fraction, nor is there any hint to (iii) subsequently elute the substrate-bound nucleic acids using a buffer having very low ionic strength.

Little provides no teaching or suggestion to supply the salient deficiencies in Henco. Almost the same distinction with Henco applies with regard to the distinguishing Little from the presently claimed process. Applicant could not find any passage in the whole disclosure of Little that nucleic acids, ***which have already been separated,*** should be subjected to a treatment according to the process of Little. Therefore, there is indeed no motivation to combine the two documents, either in modifying Little according to Henco or in modifying Henco according to Little; or that any motivation is provided in the art to look to Henco or Little as suggested by the Examiner.

Applicant respectfully submits that the combination of Henco and Little is overly simplistic. Again, Henco discloses purification of nucleic acids by an anion exchange treatment or an anion exchange separation process. The key features are binding the nucleic acid at low ionic strength and eluting the nucleic acids at concentrations in the range of 2 M salt in the buffer (the number can be derived from Fig. 4 of the specification of Henco). No use of any chaotropic salt is disclosed in Henco.

On the other hand, Little binds nucleic acids from a solution having a very high content of salts, especially chaotropic salts.

The skilled artisan would not have had any incentive to even increase the "high" salt concentration obtained after henco's process after reading Little's disclosure. The Examiner, himself, points out that Henco teaches desalting the sample obtained after the last step of the claim 1 of Henco (however, desalting is optional - "if desired" - not needed as stated by the Examiner). Optional desalting in Henco by the procedures disclosed therein is not disputed.

Applicant does dispute, however, that the skilled artisan would have been motivated to rely on Little's process in order to "desalt" Henco's sample. According to Henco, if desired, the skilled artisan would, regardless of the circumstance, try to reduce the salt content; either by applying a salt concentration, as low as possible, in the eluting step or by trying to desalt the sample by well known conservative methods, such as dialysis or gel permeation chromatography.

By no means however, would the skilled artisan ever consider, as opposed to getting rid of the salt, actually increasing after elution the salt content of the sample in Henco's process in order to obtain a sample having a very, very high salt concentration, as required in Little. The fact that, in accordance with the presently claimed invention, there is performed the step of increasing the salt content after Henco's process, in order to be able to employ process steps as disclosed in Little, may be regarded as a key unexpected step of steps as disclosed in the present invention.

Applicant respectfully submits that, on page 3 of the Official Action, paragraph 2, the Examiner mistakenly points out that Henco claim 8 would already anticipate a filtration step by saying that "mechanical procedures" would be used. However, in this context, the mechanical procedures used are for disrupting the cells; for example, a French press treatment or a mechanical disruption of the cell by tissue grinding.

Also, the comments in the outstanding action of claims 60 and 61 are not justified. The Examiner ignores the significance of the "digested" step in the context of the invention. The digestion of the cells according to the present invention is performed with proteinases, detergents or other aggressive chemicals (see page 23, last paragraph of the present specification). This

leads to a slimy mixture containing lysed cell ingredients or lysed cells. Material in a cell mixture tends to stick, not only together, but also, on filters. Such a mixture leads to clogging of conventional filters such as described in Hagen or Sternberg.

Hagen's composite material is used for pre-concentration of samples for further analysis (c.f. column 8, line 32 of that particular reference). Neither Hagen nor Sternberg teach using such devices for the filtration of a sample obtained by digestion of cells according to the presently claimed invention.

Hagen does not teach use of stacked membranes for filtering "digested" cells. Accordingly, the teaching of Hagen cannot render obvious, either alone or in combination with any other references, the claimed process of the present invention.

Applicant emphasizes that device claims are not at issue, but process claims. The Examiner's interpretation of the claims with respect to Hagen and Sternberg is, with all due respect, a matter of hindsight.

Sternberg discloses, in column 6, line 9 nothing whatsoever with respect to a process for isolation and purification of nucleic acids from a sample consisting of digested cells.

Henco apparently regarded as the closest prior art, uses a filtration step in example 2 (column 12, line 24). However, the teaching of example 2 of that reference is that at first a centrifugation step has to be performed. This means that the reference even teaches away from the teaching of the present invention; to avoid centrifugation and, instead, directly filter the samples containing digested cells.

Moreover, example 2 discloses a preparation of a λ-phage DNA. Such preparation is an exceptional procedure in the art.

The exception in the λ-phage technology is based on the fact that the λ-phage lyses its host for example an E. coli cell. Therefore, a culture being infected with λ-phages results either intact E. coli cells or if the phage is activated lysed Escherichia coli. A lysed E. coli is completely disrupted, i.e., any morphology of the former E. coli is dissolved. Therefore, a lysed E. coli could pass such conventional filters without clogging. Only if the pore size is so large that it can accept intact E. coli cells could such a sample not be filtered. However, in the case of example 2, where a mixture is used having intact E. coli and lysed E. coli cells, first of all centrifugation takes place so that the intact cells are removed, and then the supernatant is filtered. The skilled artisan knows that no clogging of the filters occurs. The situation of example 2 is in no way comparable with the sample obtained by a digestion according to the present claimed invention. The sample of example 2 of the Henco reference would never clog a narrow pore sterile filter. However, a sample prepared according to the presently claimed invention would do so.

A prominent difference between Hagen and the filtration step (a) recited in present claim 60 is the fact that the filters must not contain a matrix in which are enmeshed active sorptive non-swellable particles. The filtration step (a) is more or less conventional filtration; not combined with an absorption, but using a pore size which decreases in the flow direction. This is advantageous since such "asymmetric filters" do not clog.

The obviousness rejections of record are based, with all due respect, on analyses that are inconsistent with the appropriate standards established by statute, case law, and regulations. Concerning the combination of Henco and Little as alleged in the outstanding Official Action, Applicant respectfully submits that there is no motivation for making the combination as suggested in order to effect the presently claimed invention. Applicant observes the Examiner's argument that Henco teaches the "need" for a desalting step. On the contrary, as discussed, *supra*, desalting is an optional step in Henco ("if desired, DNA may be desalted by a) dialysis, b) precipitation or c) gel permeation chromatography"; Henco, column 7, lines 44-46). The actual teaching, therefore, of Henco is that desalting can be performed "if desired." The problem with the arguments contained in the outstanding Official Action is the failure to show, where and how, the prior art teaches that it is "desired" to desalt the material disclosed in Henco by using the separation method disclosed in Little. "The mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggested the ***desirability*** of the modification." *In re Fritsch*, 23 USPQ2d 1780, 1783-84 (emphasis added).

As discussed, *supra*, the combination of Little and Henco is contraindicated; at least in the manner suggested in the outstanding Official Action. Henco and Little disclose alternative procedures for isolating DNA from cells. Besides the factual contraindication, there is simply no art-disclosed motivation of record for effecting the ***sequential*** combination of two procedures (Henco's and Little's) previously known as ***alternative*** methods for isolating DNA from cells.

Absent the hindsight provided by the teachings of the present invention, there is no motivation to combine the known alternative procedures in a sequential manner. "When prior art references require selective combination ... to render obvious a subsequent invention, there must be some reason for the combination other than the hindsight gleaned from the invention itself. ... There must be something in the prior art to suggest the desirability, and thus the obviousness, of making the combination." *Interconnect Planning Corp. v. Feil*, 227 USPQ 543, 551 (Fed. Cir. 1985). A rejection for obviousness is improper when "the only suggestion for the Examiner's combination of the isolated teachings of the applied references improperly stems from ... [the Applicant's] disclosure and not from the applied prior art". *Ex Parte Levengood*, 28 USPQ2d 1300, 1301 (BPA&I 1993).

Regarding rejections based on combinations of teachings including Sternberg, Applicant submits that these combinations fail to address the claimed invention in its entirety. In making an obviousness determination the claimed invention must be considered as a whole. *In re Hedges*, 228 USPQ 685 (Fed. Cir. 1986). In conducting an obviousness analysis reducing the claimed invention to a gist or core is improper. *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.*, 230 USPQ 416 (Fed. Cir. 1986). It is well established that "all limitations of a claim must be considered in determining the claimed subject matter as is referred to in 35 U.S.C. §103 and it is error to ignore specific limitations distinguishing over the reference." *Ex Parte Murphy*, 217 USPQ 479, 481 (POBdApp 1982).

In the present situation, the claimed invention defines a process for isolating DNA including the step of "digesting the cells containing nucleic acids." The factual problems that

result from this failure are discussed, *supra*. From a legal standpoint failure to account for the "digesting" step and its results means that the appropriate legal standards were not observed in making the obviousness rejections at issue. The presently claimed invention was not considered as a whole, including all limitations recited therein. Applicant respectfully submits that, in applying the teachings of Sternberg, the failure to consider the digesting step in the obviousness analysis renders the rejections improper. *Hedges*; *Murphy*.

Regarding combinations involving Sternberg and Hagen Applicant observes the Examiner's argument that a variation in filter porosity (from that disclosed in Hagen or Sternberg) is "deemed" to be knowledge possessed by one of ordinary skill in the art; however, no evidence is provided in support thereof. "The Examiner should be aware that ***deeming*** does not discharge him from the burden of providing the requisite factual basis and establishing the requisite motivation to support the conclusion of obviousness." *Ex parte Stern*, 13 USPQ2d 1379, 1381 (BPA&I 1989), emphasis in original. Applicant respectfully requests that the Examiner provide either evidence or affidavit to support whatever is "deemed" to be part of the prior art [see 37 CFR §1.107(b); "An examiner's failure to support a challenged officially noticed fact with objective evidence constitutes reversible error." *Ex Parte Natalie*, 11 USPQ2d 1222 (BPA&I 1989)].

Favorable action commensurate with the foregoing is requested.

Respectfully submitted,

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